

NEURO REGENERATIVE PEPTIDES

EDWIN LEE MD, FACE
CO FOUNDER OF CLINICAL PEPTIDE SOCIETY



83 YEAR OLD WITH ALZHEIMER'S –
2015 DEPRESSION, ANXIETY WITH MEMORY LOSS ON
CONVENTIONAL MEDICAL THERAPY



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IN END OF DEC OF 2017 SHE CAME TO SEE ME IN MY OFFICE

- She was on anti depressants, anti anxiety medications and memantine (Namenda)
- Her blood work showed low on all of hormones
- She received a week of IV nutrition and IV Cerebrolysin 10 ml daily
- She got on Vitamin D, estradiol patch, progesterone and a peptide called Cerebrolysin 1 ml IM 5 times a week when she went home



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87 YEAR OLD WITH SIGNIFICANT IMPROVEMENT — 2019 TURNED 87 WITH HER 10TH GRANDSON



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2019 A LITTLE OVER 1 YEAR LATER- 87 years old



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NOOTROPIC AGENT

- Substance that enhances cognition and memory and facilitates learning
- Cerebrolysin
- TB4
- Semax
- Selank



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CEREBROLYSIN

- Discovered by an Austrian professor Gerhart Harrer in 1949
- Mixture of many neuropeptides and amino acids
- Enzymatic hydrolysis of the young pig brain tissue produces substances that can stimulate nerve cells.



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CEREBROLYSIN

BERK, C., & SABBAGH, M. N. (2013). SUCCESSES AND FAILURES FOR DRUGS IN LATE-STAGE DEVELOPMENT FOR ALZHEIMER'S DISEASE. *DRUGS & AGING*, 30(10), 783–792. DOI:10.1007/S40266-013-0108-6

- Cerebrolysin is currently approved for use in over 50 countries as a treatment for dementia and stroke
- Approved for use in Austria, China, Germany, Russia and South Korea
- Not FDA approved in the US

Cerebrolysin®



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CEREBROLYSIN CONTAINS

- Glial cell line derived neurotrophic factor (GDNF)
- Nerve growth factor (NGF)
- Ciliary neurotrophic factor (CNTF)
- Menon PK, et al. [CNS Neurol Disord Drug Targets](#). 2012 Feb;11(1):40-9.

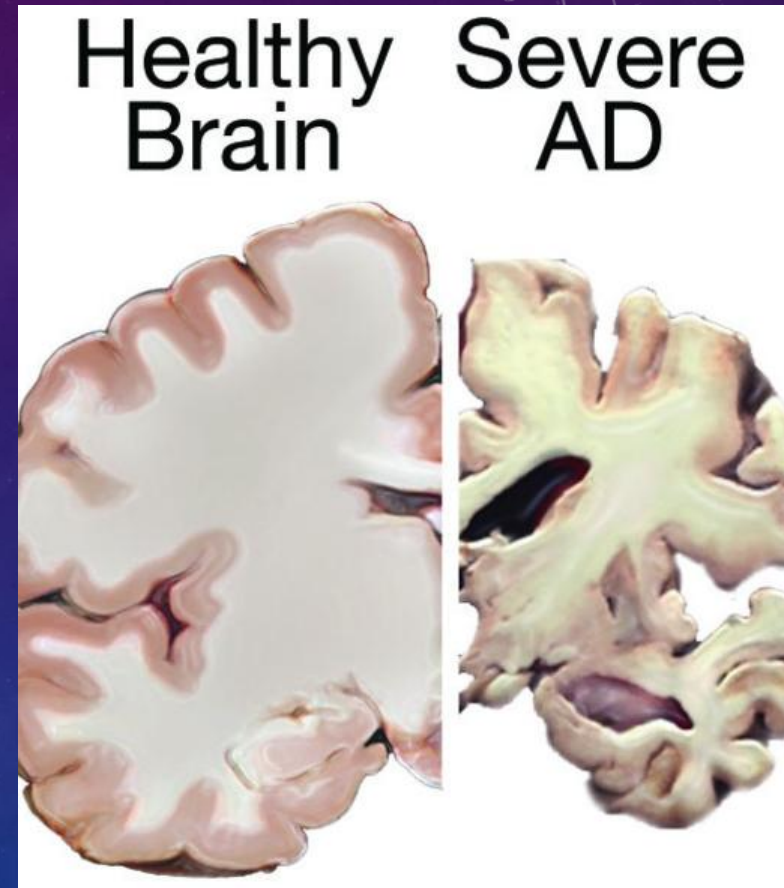


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CEREBROLYSIN

- Meta-Analysis of 6 randomized double-blind placebo-controlled studies on 30 ml/day of Cerebrolysin in mild-to-moderate AD
- All Studies had 20 IV infusion of 30 ml of Cerebrolysin during the first month
- Gauthier S, et al (2015) Cerebrolysin in mild-to-moderate alzheimer's disease: a meta-analysis of randomized controlled clinical trials. Dement Geriatr Cogn Disord 39:332–347.



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RESULTS OF 6 STUDIES USING CEREBROLYSIN

GAUTHIER S, ET AL (2015) CEREBROLYSIN IN MILD-TO-MODERATE ALZHEIMER'S DISEASE: A META-ANALYSIS OF RANDOMIZED CONTROLLED CLINICAL TRIALS. DEMENT GERIATR COG

- Mean age 72 years old
- Cerebrolysin was significantly more effective than placebo at 4 weeks and 6 months regarding cognitive function



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CEREBROLYSIN WITH ARICEPT

ALVAREZ X, ET AL *INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY*, (2016) 19(6): 1–6

- Low BDNF has been associated with Alzheimer's disease
- Recent 2016 Randomized double blind trial showed Cerebrolysin increases BDNF
- Combination of Cerebrolysin with donepezil (acetylcholinesterase inhibitor) increases BDNF



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CEREBROLYSIN WITH APO E4

ALVAREZ X, ET AL *INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY*, (2016) 19(6): 1–6

- BDNF increases were greater in apolipoprotein E4 allele carriers
- Higher BDNF levels were associated with better cognitive improvements



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CEREBROLYSIN IN FIRST DEGREE RELATIVES WITH ALZHEIMER'S

- 67 relatives with minimal cognitive dysfunction (mean age 57.6)
- IV Cerbrolysin 20 ml/d
- Treatment was 1 month
- Improvement in cognition
- Selezneva ND, et al. [Zh Nevrol Psikhiatr Im S S Korsakova](#). 2018;118(10):30-36.



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Review > [Drugs Today \(Barc\)](#). 2012 Apr;48 Suppl A:25-41.

doi: 10.1358/dot.2012.48(Suppl.A).1739721.

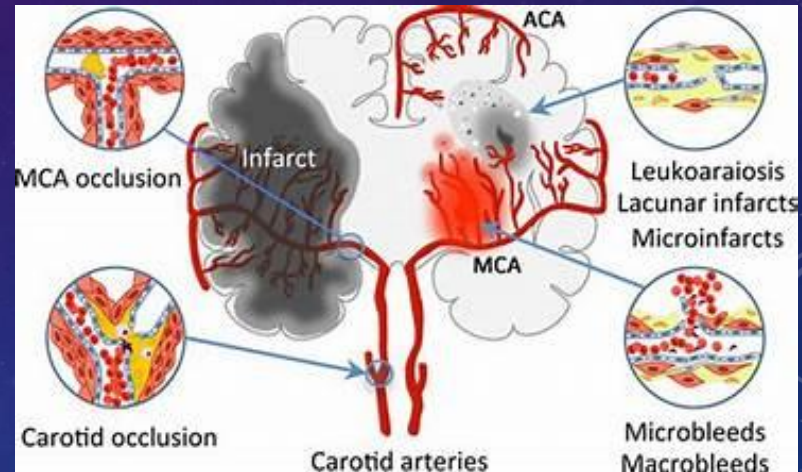
Cerebrolysin improves symptoms and delays progression in patients with Alzheimer's disease and vascular dementia

R F Allegri ¹, A Guekht

VASCULAR DEMENTIA

GUEKHT AB, ET AL. CEREBROLYSIN INVESTIGATORS. CEREBROLYSIN IN VASCULAR DEMENTIA: IMPROVEMENT OF CLINICAL OUTCOME IN A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER TRIAL. J STROKE CEREBROVASC DIS. 2011 JUL-AUG;20(4):310-8

- Multicenter, double-blind, placebo-controlled study in 242 patients with vascular dementia
- 24 weeks of treatment
- Intravenous Cerebrolysin 20 mL was administered once daily over the course of 2 treatment cycles



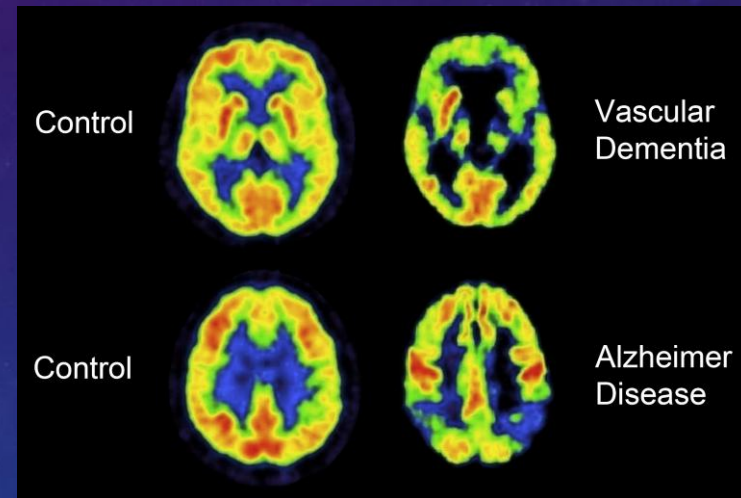
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VASCULAR DEMENTIA

GUEKHT AB, ET AL. CEREBROLYSIN INVESTIGATORS. CEREBROLYSIN IN VASCULAR DEMENTIA: IMPROVEMENT OF CLINICAL OUTCOME IN A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER TRIAL. J STROKE CEREBROVASC DIS. 2011 JUL-AUG;20(4):310-8

- Cerebrolysin significantly improved clinical outcome in vascular dementia
- Cerebrolysin was safe and well tolerated.



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TREATMENT WITH CEREBROLYSIN FOR ACUTE STROKE

LADURNER G, ET. AL ; CEREBROLYSIN STUDY GROUP. NEUROPROTECTIVE TREATMENT WITH CEREBROLYSIN IN PATIENTS WITH ACUTE STROKE: A RANDOMISED CONTROLLED TRIAL. J NEURAL TRANSM (VIENNA). 2005 MAR;112(3):415-28.

- Randomized placebo trial
- N = 148
- 50 ml/day x 21 days
- Cerebrolysin was well tolerated and safe
- Significant improvement of cognitive function of the patients on Cerebrolysin was observed in the Syndrome Short Test when compared to the placebo group.
- No improvement in the Canadian Neurological Scale and others



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ANOTHER STUDY WITH CEREBROLYSIN FOR ACUTE STROKE

GHARAGOZLI K, ET AL.. EFFICACY AND SAFETY OF CEREBROLYSIN TREATMENT IN EARLY RECOVERY AFTER ACUTE ISCHEMIC STROKE: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLINDED, MULTICENTER CLINICAL TRIAL. J MED LIFE. 2017 JUL-SEP;10(3):153-160.

- Randomized double blind trial
- N = 100
- 30 ml IV daily for 7 days then 10 ml IV daily x 30 days
- At the end of 30 days significant improvement in the National Institutes of Health Stroke Scale and Clinical Global Impression



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USED IN OVER 50 COUNTRIES – INCLUDING MEXICO

Review > [Neurol Sci.](#) 2021 Apr;42(4):1345-1353. doi: 10.1007/s10072-021-05089-2.

Epub 2021 Jan 30.

Cerebrolysin for stroke, neurodegeneration, and traumatic brain injury: review of the literature and outcomes

Brian Fiani ¹, Claudia Covarrubias ², Amelia Wong ³, Thao Doan ⁴, Taylor Reardon ⁵,
Daniel Nikolaidis ⁶, Erika Sarno ⁷

Cerebrolyin for aphasia

Randomized Controlled Trial > [Stroke](#). 2025 Apr;56(4):937-947.

doi: 10.1161/STROKEAHA.124.049834. Epub 2025 Feb 17.

Speech Therapy Combined With Cerebrolysin in Enhancing Nonfluent Aphasia Recovery After Acute Ischemic Stroke: ESCAS Randomized Pilot Study

Volker Homberg¹, Dragoş Cătălin Jianu^{2 3 4}, Adina Stan^{5 6}, Ştefan Strilciuc^{7 6},
Vlad-Florin Chelaru^{5 6}, Michał Karliński⁸, Michael Brainin⁹, Wolf Dieter Heiss¹⁰,
Dafin F Muresanu^{5 6}, Pamela M Enderby¹¹

Affiliations + expand

PMID: 39957612 PMCID: [PMC11932442](#) DOI: [10.1161/STROKEAHA.124.049834](#) 

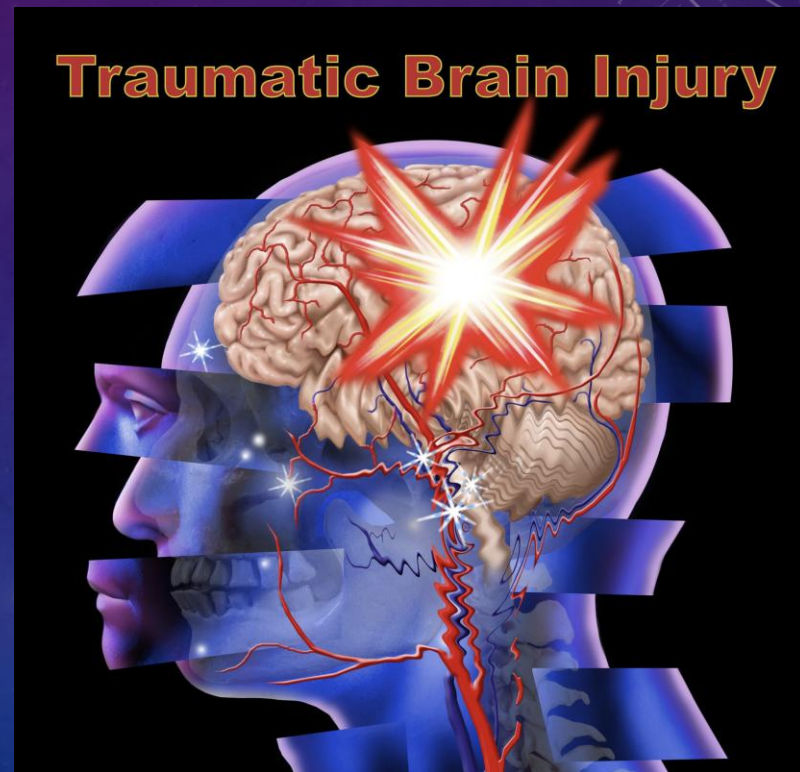
Cerebrolyin 30 ml IV x 10 days with 1 hour speech therapy x 10 days –
3 cycles (1 to 14, 29 to 42, and 57 to 70)

Cerebrolyin with speech therapy improved aphasia and functional independence

CEREBROLYSIN FOR TRAUMATIC BRAIN INJURY (TBI)

JAROSZ K, ET. AL., CEREBROLYSIN IN PATIENTS WITH TBI: SYSTEMATIC REVIEW AND META-ANALYSIS. BRAIN SCI. 2023 MAR 17;13(3):507.

- Meta-analysis of 10 studies
- 8749 patients
- Cerebrolysin treatment improved the clinical outcome of patients after TBI



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CEREBROLYSIN USED IN INFANTS

Review > [Acta Neurol Belg.](#) 2021 Dec;121(6):1401-1406. doi: 10.1007/s13760-021-01795-y.

Epub 2021 Sep 8.

Neuroprotective strategies of cerebrolysin for the treatment of infants with neonatal hypoxic-ischemic encephalopathy

Brian Fiani ¹, Daniel Chacon ², Ryan Jarrah ³, Michaela Barthelmass ⁴, Claudia Covarrubias ⁵

Cerebrolysin injections of 0.1 ml/kg of body weight twice per week were found to provide gross motor and speech deficit improvement.



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CEREBROLYSIN DOSING

STAN A, ET AL., CEREBROLYSIN AND EARLY NEUROREHABILITATION IN PATIENTS WITH ACUTE ISCHEMIC STROKE: A PROSPECTIVE, RANDOMIZED, PLACEBO-CONTROLLED CLINICAL STUDY *JOURNAL OF MEDICINE AND LIFE* VOL. 10, ISSUE 4, OCTOBER-DECEMBER 2017, PP.216-222

- Dosing used in studies were 10- 30 ml/ day IV 5 days a week.
- Concentration is 215.2 mg/ml
- Comes in 10 ml ampules
- Optional dosing
- Infuse 30 ml (6456 mg) in 250 cc of normal saline over 1 hour 2-3 times a week. Recommend using a filter
- 1 ml (215.2 mg) IM shot 3-5 times a week

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EXPERIMENTAL DOSING FOR OPTIMAL BRAIN FUNCTION

- Cerebrolysin comes in a 10 ml ampule, inject 1 ml IM once a week to 2-3 times a week.
- The rest of the 9 ml draw up with a needle and syringe with use a filter. Store in a sterile vial (amber vial) for multiuse



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NOOTROPIC AGENT

- Substance that enhances cognition and memory and facilitates learning
- Cerebrolysin
- TB4
- Semax
- Selank



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THYMSOIN BETA 4 (TB4) myelination

MICHAEL CHOPP & ZHENG GANG ZHANG (2015) THYMOSIN B4 AS A RESTORATIVE/ REGENERATIVE THERAPY FOR NEUROLOGICAL INJURY AND NEURODEGENERATIVE DISEASES, EXPERT OPINION ON BIOLOGICAL THERAPY, 15:SUP1, 9-12

- Thymosin B4 promotes CNS and peripheral nervous system (PNS) myelination.

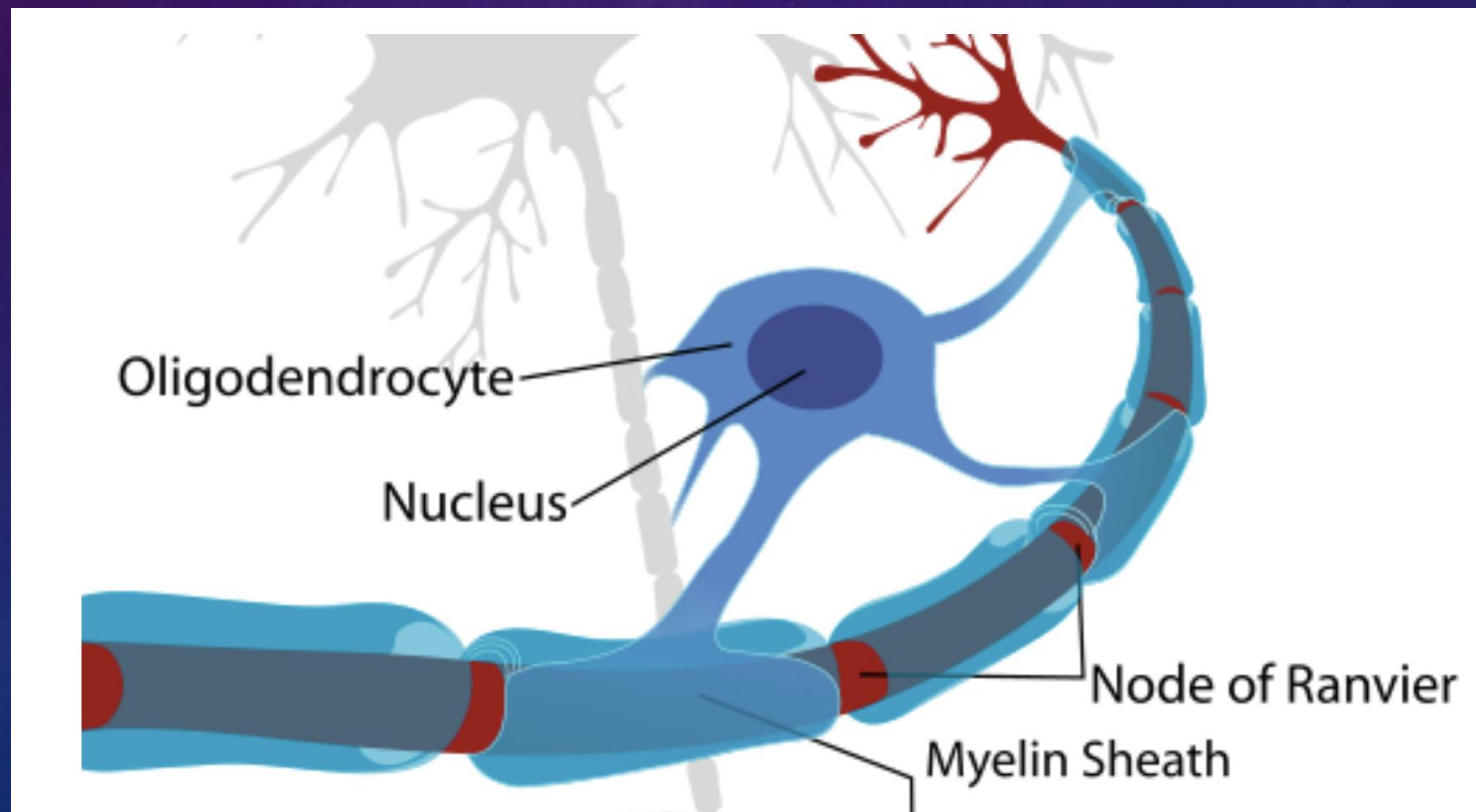


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Thymosin beta 4 mediates oligodendrocyte differentiation by upregulating p38 MAPK

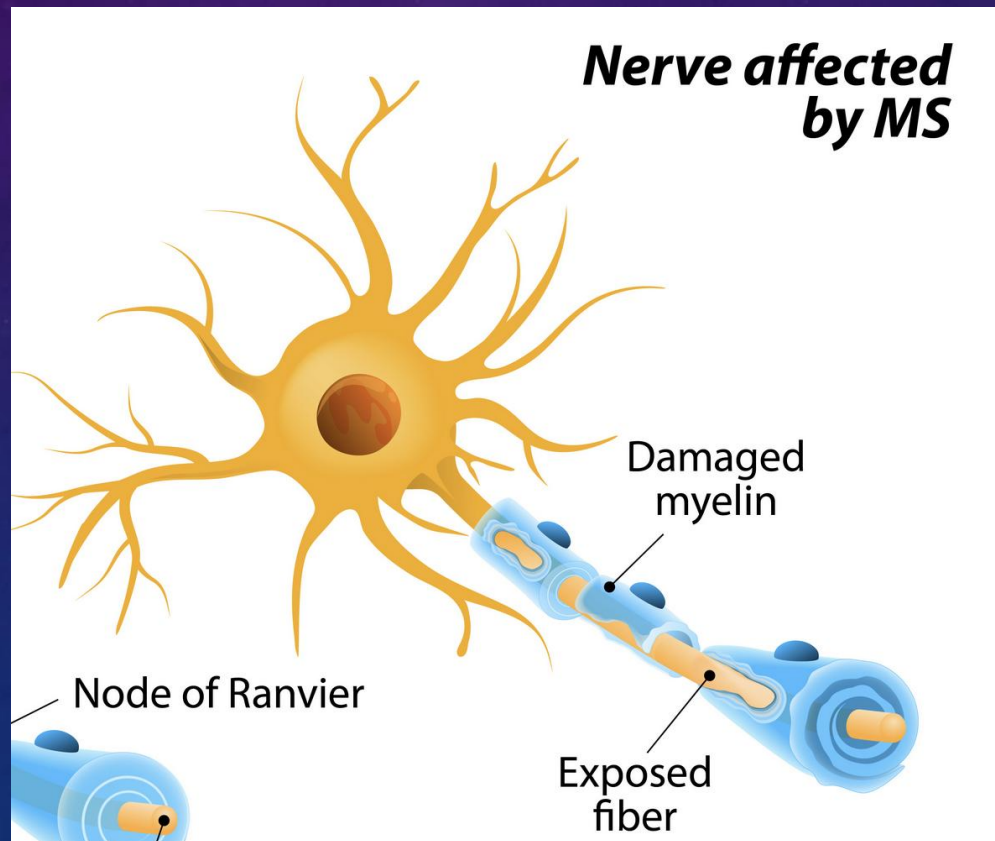
[Manoranjan Santra](#)¹, [Michael Chopp](#)^{1,3}, [Zheng Gang Zhang](#)¹, [Mei Lu](#)⁴, [Sutapa Santra](#)¹, [Ankita Nalani](#)¹, [Soumi Santra](#)¹, [Daniel C Morris](#)²



> [Neurobiol Dis.](#) 2016 Apr;88:85-95. doi: 10.1016/j.nbd.2016.01.010. Epub 2016 Jan 12.

Thymosin beta4 promotes oligodendrogenesis in the demyelinating central nervous system

Jing Zhang¹, Zheng Gang Zhang², Yi Li², Mei Lu³, Yi Zhang², Stanton B Elias², Michael Chopp⁴



THYMSOIN BETA 4 dosing

- Comes in 3000 mcg/ml
- Can give it SQ or IV Push
- For acute injury use $\frac{1}{2}$ ml (1500 mcg) to 1 ml – 3000 mcg IVP or SQ daily to BID for 3-5 days
- Reduce it to $\frac{1}{4}$ cc or 750 mcg SQ daily for 20- 30 days



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WHAT HAPPENS IF YOU CAN'T GET TB4?

- Thymosin beta 4 frag
- It is the bioactive part of TB4
- 4 amino acid vs 43 AA
- Acetyl-N-Ser-Asp-Lsy-Pro (AsSDKP)
- Comes in a pill – 500 mcg a day
- FDA ban on TB4 fragment is (LKKTETQ) – 7 Amino acid



TB4 FRAGMENT

> [Neuroscience](#). 2015 Dec 3;310:51-62. doi: 10.1016/j.neuroscience.2015.09.017. Epub 2015 Sep 9.

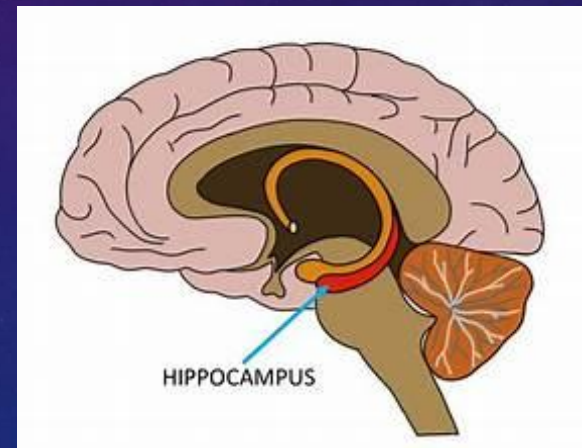
Peptide fragment of thymosin β 4 increases hippocampal neurogenesis and facilitates spatial memory

D H Kim ¹, E-Y Moon ², J H Yi ³, H E Lee ⁴, S J Park ⁴, Y-K Ryu ⁵, H-C Kim ⁶, S Lee ⁷,
J H Ryu ⁸

TB4 FRAGMENT - INCREASES NEUROGENESIS

KIM DH, ET AL., PEPTIDE FRAGMENT OF THYMOSIN B4 INCREASES HIPPOCAMPAL NEUROGENESIS AND FACILITATES SPATIAL MEMORY. NEUROSCIENCE. 2015 DEC 3;310:51-62

- Mice study
- Intrahippocampal infusion of TB4 frag facilitated the generation of new neurons in the hippocampus



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TB4 FRAGMENT - INCREASES NEUROGENESIS

KIM DH, ET AL., PEPTIDE FRAGMENT OF THYMOSIN B4 INCREASES HIPPOCAMPAL NEUROGENESIS AND FACILITATES SPATIAL MEMORY. NEUROSCIENCE. 2015 DEC 3;310:51-62

- Intrahippocampal infusion of TB4 frag also increased spatial memory.
- TB4 frag may be a therapeutic candidate for diseases characterized by neuronal loss.



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EXTRA NOOTROPIC AGENT

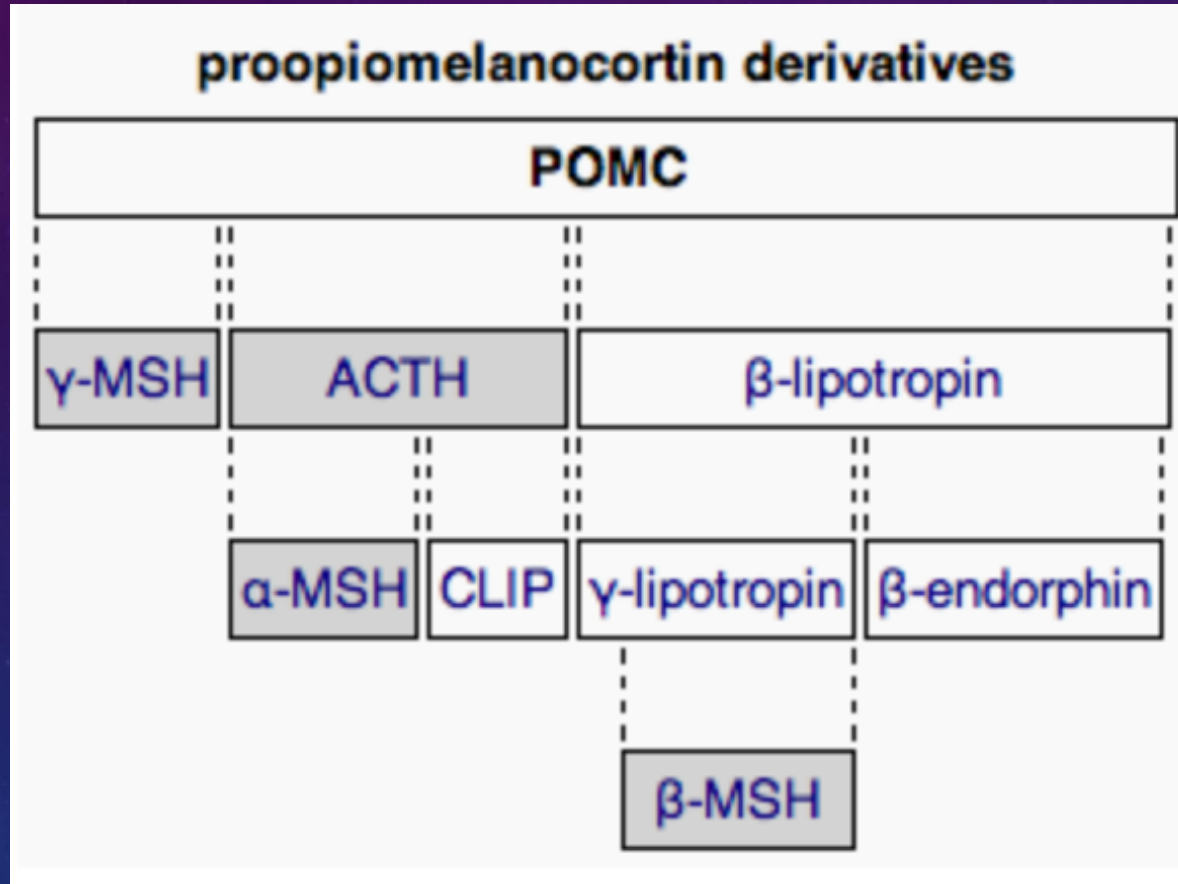
- Semax



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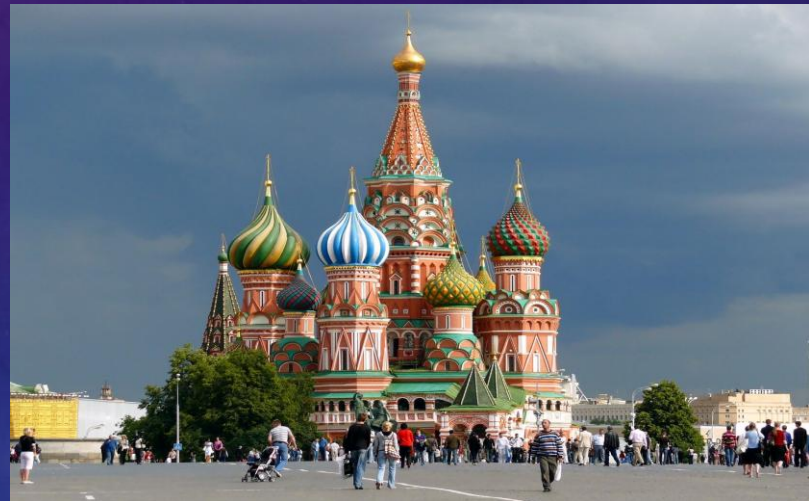


SEMAX (7 AMINO ACID ANALOG TO ACTH 4-10)



SEMAX (ANALOGUE OF ACTH (4-10))

- Discovered and research in Russia (unfortunately a lot of studies are all in Russian without an abstract)
- 7 Amino acid
- Has no hormonal activity
- Tsai SJ. [Med Hypotheses](#). 2007;68(5):1144-6. Epub 2006 Sep 25.



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SEMAX (ANALOGUE OF ACTH (4-10))

- Study in rat brains occluding the middle cerebral artery
- Shown to increase brain-derived neurotrophic factor (BDNF), NGF (Nerve growth factor) TrkB (tyrosine kinase receptor type 2)
- Tyrosine kinase receptor type 2 (TrkB), which has the highest affinity for brain-derived neurotrophic factor (BDNF) and is involved in neuronal plasticity

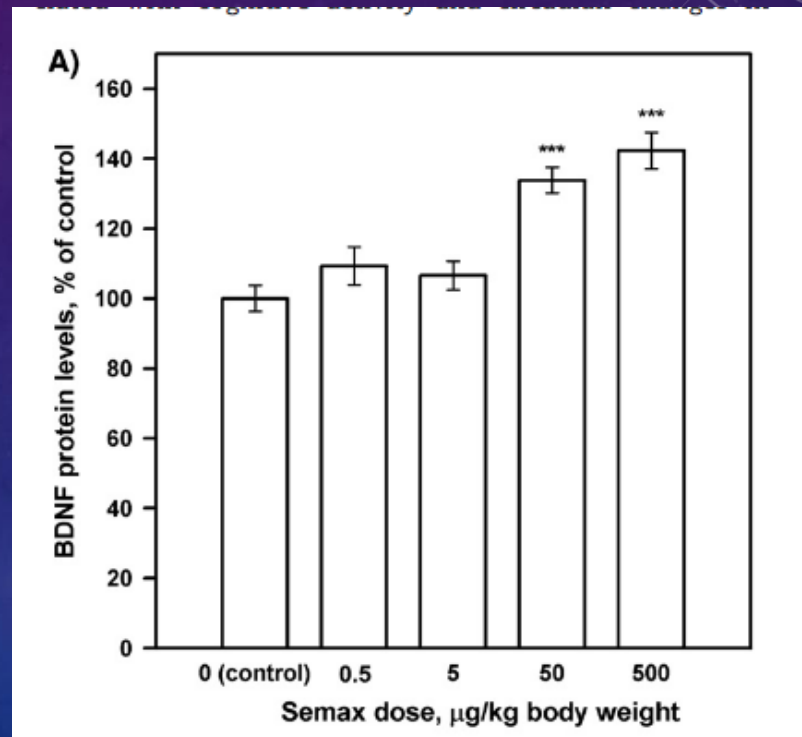
• Dmitrieva VG, et al. [Cell Mol Neurobiol.](#) 2010 Jan;30(1):71-9

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SEMAX intranasal increases BDNF & TrkB)

- Study in rats given a single application of Semax (50 μ g/kg body weight) results in a increase of BDNF and TrkB
- Dolotov OV, et al. Semax, an analog of ACTH(4–10) with cognitive effects, regulates BDNF and trkB expression in the rat hippocampus. BRAIN RESEARCH 1117 (2006) 54–60



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SEMAX IN STROKE

- Study of 30 patients with acute ischemic stroke
- Semax improved in the recovery of stroke clinically and by EEG
- 12 mg for moderate stroke
- 18 mg for severe stroke
- Tx course--5 and 10 days
- Gusev EI, et al. [Zh Nevrol Psikhiatr Im S S Korsakova. 1997;97\(6\):26-34](#)



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Use of the Neurospecific Peptide Substance "Semax" in the Acute Period of Ischemic Stroke

E. I. Gusev, V. I. Skvortsova, E. Yu. Zhuravleva, A. V. Vanichkin
Russian State Medical University, Moscow

Gusev EI, Skvortsova VI, Zhuravleva EYu, Vanichkin AV. **Usage of neurospecific peptide substance "Semax" in acute period of ischemic insult.** *Neurology Bulletin (Nevrologicheskiy Vestnik)*. 1997;29(3–4):32–38. doi:10.17816/nb80150.

ANOTHER STUDY OF SEMAX IN STROKE

GUSEV EI, ET.AL. USAGE OF NEUROSPECIFIC PEPTIDE SUBSTANCE "SEMAX" IN ACUTE PERIOD OF ISCHEMIC INSULT. *NEUROLOGY BULLETIN (NEVROLOGICHESKIY VESTNIK)*. 1997;29(3-4):32-38.
DOI:10.17816/NB80150.

- 110 patients with ischemic stroke
- Mean age of 69.6 years
- 30 used Semax
- 80 in the control group
- Semax daily doses of 12, 18, and 24 mg intranasal x 5 days
- Noted that in 5 patients did better if they did 10 days of Semax

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ANOTHER STUDY OF SEMAX IN STROKE

GUSEV EI, ET.AL. USAGE OF NEUROSPECIFIC PEPTIDE SUBSTANCE "SEMAX" IN ACUTE PERIOD OF ISCHEMIC INSULT. *NEUROLOGY BULLETIN (NEVROLOGICHESKIY VESTNIK)*. 1997;29(3-4):32-38.
DOI:10.17816/NB80150.

- Conclusion with Semax therapy- improved the recovery of impaired neurologic functions.
- The authors noted that a 10-day course of Semax vs 5 days would be ideal
- 12 mg for moderate stroke
- 18 mg for severe stroke



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SEMAX

- Semax has a poor oral delivery
- Can be delivered by Subcutaneous or intranasal
- Suggested dosing
- 750 mcg per nasal spray in each nostril once a day. (total dose of 1500 mcg)
- The stroke studies used up 18 mg a day



ANOTHER EXTRA NOOTROPIC AGENT

- Selank

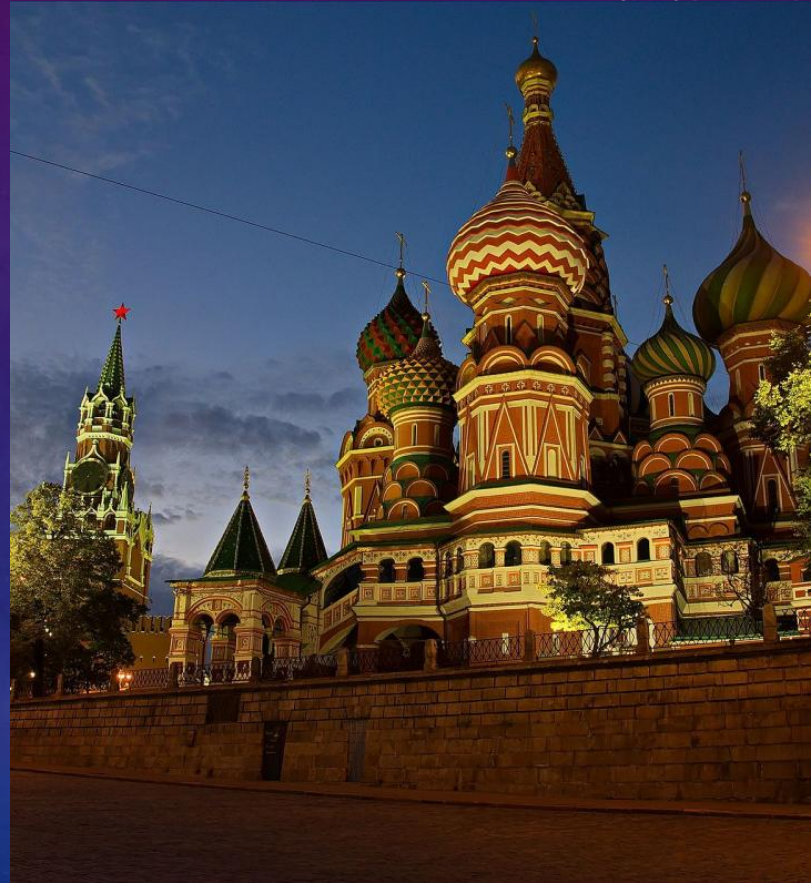


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SELANK

- Discovered and research in Russia (unfortunately a lot of studies are all in Russian without an abstract)
- 7 Amino acid
- It is a synthetic analogue of human tuftsin. (part of the Fc domain of IgG)



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SELANK

Zozulia AA, et al. Efficacy and possible mechanisms of action of a new peptide anxiolytic selank in the therapy of generalized anxiety disorders and neurasthenia. ZH NEVROL PSIKHIATR IM S S KORSAKOVA. 2008;108(4):38-48.

- Main effect is that it helps with anxiety
- Study of 62 patients with Generalized Anxiety Disorder, Selank reduced anxiety without having any sedative properties



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SELANK

Inozemtseva LS, et al. Intranasal administration of the peptide selank regulates BDNF expression in the rat hippocampus in vivo. DOKL BIOL SCI. 2008 JUL-AUG;421:241-3.

Zozulya AA, et al. The inhibitory effect of selank on enkephalin-degrading enzymes as a possible mechanism of its anxiolytic activity. BULL EXP BIOL MED. 2001 APR;131(4):315-7.

- Selank increases BDNF in rats
- Selank have been found to inhibit enzymes involved in the degradation of enkephalins (which may be the mechanism of action for the anxiolytic activity)

Anxiolytics



SELANK AFFECTS GENE EXPRESSION

- Study on Rats
- Three hours after Selank administration, 22 genes changed their expression of GABAergic system (transporter of GABA and GABA receptors)



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SELANK

- Selank has a poor oral deliverly
- Can be delivered by Subcutaneous or intranasal
- Suggested dosing
- 75 μg of Selank per nasal spray. The recommended dosage is 1-2 sprays per dose with 2- 3 doses per day (a max total of 675 $\mu\text{g}/\text{day}$)



CONCLUSION OF NOOTROPIC AGENT

- Cerebrolysin increases BDNF
- Semax increases BDNF
- Selank increases GABA
- TB4 increases myelination



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**THANK
YOU!**